

REMARKS

Applicant respectfully requests reconsideration. Claims 26-48 were previously pending in this application. Claim 26 is amended herein. As a result, claims 26-48 are still pending for examination with claims 26 and 38 being independent claims. No new matter has been added.

Interview Summary

Applicant and the under-signed attorney thank Examiner Gussow for the telephone interview of December 8, 2008. During the interview, Examiner Gussow and Applicant's representative discussed the main objection in the outstanding Office Action, which pertains to whether the use of oligonucleotides that are not antisense is supported in the application.

Rejection Under 35 U.S.C. 112

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking written description. The Examiner has dismissed the arguments presented by Applicant and alleged that "Applicant was not in possession of the broad genus of oligonucleotides that are encompassed by not antisense since the disclosure describes antisense molecules." (Office Action p. 8) Applicant respectfully traverses the rejection.

Applicant has disclosed in the specification several phosphorothioate oligonucleotide analogs and their use in promoting cell mediated and local immune responses apart from their ability to produce antisense effect. For example, ISIS 1082 (Seq ID NO: 2) described in the specification is a 21-mer phosphorothioate oligonucleotide analog targeted to the translation initiation codon for the UL13 gene of Herpes Simplex Virus (HSV). ISIS 1082 is an antisense ODN but the immune stimulatory effects of the ODN observed in the Examples are not antisense specific. Repeated intradermal administration of this oligonucleotide to healthy rats with no HSV infections was shown to elicit a local immune response and resulted in the release of cytokines. Thus, even though the rats were not infected with HSV, the HSV antisense ODN (1082) had an immune stimulatory effect. Similarly, repeated administration of ISIS 2105 (Seq ID NO: 1) designed to inhibit the replication of HPV types 6 and 11, to healthy uninfected rats significantly enhanced the humoral response. Incubation of this oligonucleotide analog or ISIS 1082 with an uninfected *in vitro*

human skin model derived from neonatal keratinocytes and fibroblasts resulted in a concentration dependent increase of cytokine release. Given the absence of any viral infections in the rats and the skin model used in these studies, these examples demonstrate the ability of the claimed oligonucleotides to induce an immunostimulatory response that is unrelated to any antisense effect. Furthermore, in human clinical trials, intradermal injections of ISIS 2105 to healthy male volunteers induced an immune response that was shown to involve both T-cell and B-cell activation. Thus, the data in the specification established that the claimed oligonucleotides can produce a cell-mediated immune response that is not related to any antisense effect which these oligonucleotides may or may not possess.

The Examiner has alleged that "one of ordinary skill in the art would not expect all possible phosphorothioate oligonucleotide analogs, or even a representative number, to induce cell mediated or local immune responses." According to the MPEP 2163, "[a]n adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000)". At the time of filing of the instant application, oligonucleotides containing phosphorothioate modifications were well known in the art. Applicant has disclosed several working examples that demonstrate the ability of such oligonucleotides to induce cell-mediated and local immune responses, irrespective of their antisense effects. The specification describes both structure (an oligonucleotide with at least one phosphorothioate bond) and structure/function correlation (an oligonucleotide with at least one phosphorothioate bond induces an immune response). Applicants have demonstrated possession of a class of compounds (oligonucleotides containing phosphorothioate modifications) which can be used according to the methods of the invention. Accordingly, the written description for the claimed methods is met and it is respectfully requested that the rejection be withdrawn.

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner has alleged that the "data provided is not commensurate in scope with the claims which are drawn to methods of stimulating an immune response using any

phosphorothioate oligonucleotide analogs which are not antisense.” (Office Action p. 9-10)
Applicants respectfully disagree.

As discussed above in the response to the 112, written description rejection, Applicant has established that the claimed oligonucleotides, apart from their ability to produce antisense effects, can produce a cell-mediated immune response. The Examiner further alleges that “the specification demonstrates an immune response by administering only one antisense phosphorothioate, ISIS 2105 in rats (Example 7, pages 23 and 24), mice (Example 8, pages 24 and 25) and humans (Examples 9-11, pages 25 and 26)”. (Office Action p. 10). “The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.” In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). MPEP 2164.02. The specification describes a class of oligonucleotides containing phosphorothioate modifications that can induce cell mediated immune responses. These oligonucleotides were well known in the art at the time of filing of the instant application. Furthermore, as noted by the Office, the specification does provide data on several oligonucleotides (ISIS 2105, 1082 and 2503) which were shown to induce cell mediated immune responses in *in vitro* and *in vivo* animal models (pages 15- 26).

The Examiner has repeatedly cited Ratajczak et al. as teaching that the “administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered”. (Office Action p. 6) As stated previously, evaluation of splenomegaly and stimulation of B lymphocyte proliferation is one way of measuring a humoral immune response. A cell-mediated immune response may be evaluated, for instance, by measuring production of inflammatory cytokines such as IL-2, IFN γ , and TNF β . Applicant has demonstrated efficacy of a phosphorothioate oligonucleotide analog in both antibody production and cytokine production. The instant claims are directed to cell-mediated immune responses. The efficacy of the phosphorothioate oligonucleotide analog in eliciting a cell-mediated immune response has been demonstrated in the Examples.

The Examiner has cited Vollmer et al., McCluskie et al. and Jones et al. to demonstrate that administering any phosphorothioate oligonucleotides is unpredictable. Applicant again points out that the results of Vollmer et al. are dosage-specific and that there is an optimal dose for the activity

of T-rich nucleic acids which may not be reflected in the data of Vollmer et al. Applicant on the other hand, has demonstrated that several phosphorothioate oligonucleotide analogs (ISIS 2105, 1082 and 2503), apart from their antisense effects, can induce cell mediated responses both in *in vitro* and *in vivo* models. Additionally, the fact that some phosphorothioate nucleotide analogs may be less immunostimulatory than other CpG ODNs under certain conditions is not relevant to patentability. At the time of Applicant's invention these post-filing references regarding immunostimulatory motifs were not available to the public. Applicant is only required to show that the claimed method achieves its intended result, and not that it is more successful than other methods. Applicant has met this burden by demonstrating that phosphorothioate nucleotide analogs are immunostimulatory.

Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 26-48 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement. The Examiner alleges that the specification "does not reasonably provide enablement for stimulating an immune response with just any phosphorothioate oligonucleotide that is not antisense by just any route of administration."

As discussed above in the response to the 112, written description and enablement rejections, Applicant has established that the claimed oligonucleotides, apart from their ability to produce antisense effects, can produce a cell-mediated immune response. Several oligonucleotides (ISIS 2105 and 1082), that are complementary to viral proteins, were shown to induce cell mediated immune responses both in *in vitro* and *in vivo* animal models (pages 15- 26). Given the absence of any viral infections in the model systems used in these studies, these immune responses were found to be unrelated to antisense effects that these oligonucleotides may or may not possess. Moreover, as discussed above in the response to the 112 enablement rejection, working examples are not required to demonstrate compliance with the enablement requirement if the invention can be practiced by one of skill in the art without undue experimentation. MPEP 2164.02. Phosphorothioate oligonucleotides were well know in the art at the time of filing the instant application thereby allowing one of skill in the art to practice the invention without any undue experimentation.

The Examiner has further alleged that “[t]here is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to induce an immune response” by different routes of administration of any phosphorothioate oligonucleotide. Applicants respectfully disagree. The Examiner has cited Smith et al. for teaching that “oral administration would be affected by specialized antigen presenting cells that induce tolerance to an antigen rather than an immune response”. (Office Action p. 14). Additionally, Staines et al. was cited for teaching that “the eye is considered an immune privileged site in that there is a physiologic mechanism which protects it against pathogens and inflammation.” (Office Action p. 14) The teachings of neither Smith et al. nor Staines et al. are sufficient to contradict the teachings of the instant application that administration of phosphorothioate oligonucleotides by different routes promote cell mediated immune responses. There is no teaching or suggestion in Smith et al. that oral administration of phosphorothioate oligonucleotides can induce tolerance rather than an immune response. Similarly, Staines et al. have not demonstrated that phosphorothioate oligonucleotide administered to the eye would be unable to induce cell mediated immune responses. Solely, in order to advance prosecution Applicant has removed the limitation of ophthalmic delivery from claim 26. Thus, none of the cited reference have established that the inability of the oligonucleotides of the claimed invention to induce cell mediated immune responses.

At the time the patent application was filed, several studies characterizing the bioavailability of phosphorothioate oligonucleotides had been published. For example, Agrawal et al. Biochemical Pharmacology, Vol. 50, No. 4, page 571-576 describes the absorption, tissue distribution and *in vivo* stability of oligonucleotide analogs in rats following oral administration. The abstract teaches that “the hybrid oligonucleotide was absorbed intact through the gastrointestinal tract, indicating the possibility of oral administration of oligonucleotides, a finding that may be important in the development of antisense oligonucleotides as therapeutic agents.” Crooke, 1998, Basic Principles of Antisense therapeutics Chapter 1 is a review article that describes the progress in antisense technology and its applications. Specifically, it is taught that “Phosphorothioate oligonucleotides are rapidly and extensively absorbed after parenteral administration.” Agrawal et al. 1995, Clinical Pharmacokinetics, 28(1) pages 7-16 describes the pharmacokinetics of antisense oligonucleotides. It

was found that phosphorothioate oligonucleotides were distributed into most of the organs of animals following intravenous administration.

The above described references were published prior to or around the priority date of the instant application. These references establish that one of skill in the art would have recognized the oligonucleotide analogs can be effectively administered by various routes. Thus, at the time of the invention the data presented in the specification would have been sufficient to demonstrate to one of skill in the art that oligonucleotide analogs administered by different routes can be used for promoting cell mediated immune responses.

Accordingly, withdrawal of the rejection is respectfully requested.

Objection to Specification

The Examiner has maintained the objection to the specification for failing to provide antecedent basis for the phrase "wherein the phosphorothioate oligonucleotide is not antisense." The rejection has been maintained because the "structure of the molecule as disclosed is antisense, but the structure of the molecule as claimed is not antisense."

As discussed in the response to the rejection the 112, written description rejection, Applicant has established that the claimed oligonucleotides, apart from their ability to produce antisense effects, can produce a cell-mediated immune response. Furthermore, as stated in Applicant's previous response, the specification teaches that "It has now been found, surprisingly, that oligonucleotide analogs having at least one phosphorothioate bond can induce stimulation of a local immune response. *This immunostimulation does not appear to be related to any antisense effect which these oligonucleotide analogs may or may not possess.*" Applicant had clearly recognized in the specification that the immunostimulatory ability of the claimed oligonucleotides is not related to any antisense effect which these oligonucleotides may or may not possess.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

Claims 26, 28, 29 and 30 have been rejected as being unpatentable over claims 1-8 of U.S. Patent 6,727,230 (Hutcherson, et al.) in view of U.S. Patent 5,356,882 (Walker et al.).

Applicants state for the record that they may consider filing a Terminal Disclaimer if some of the claims are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.


CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1037.70049US00US00

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